REMARKS

The Official Action of June 16, 2008 and the art cited therein have been carefully considered. The amendments and remarks herein are considered to be responsive thereto.

I. Status of the Claims

After entry of these amendments, claims 1, 2, 7-9, 11-20, 22, 24-31, 33-40, and 43-45 are pending. Claims 1, 7-9, 11, 22, 24-31, and 45 are amended. Claims 3-6, 10, 21, 23, 32, 41, 42, and 46-58 are canceled. Claims 33, 38, and 43 have been allowed. No new claims have been added.

Claims 1 and 37 are amended to address rejections under 35 USC 112 for typographical errors in the use of subscript/superscript font. Claims 7-9, 11, 22, and 31 are amended to correct similar typographical errors.

Claim 1 is amended to overcome a rejection under 35 USC 102(a).

Claim 45 is amended to correct a typographical error, replacing "42" with "44." Support for this correction can be found on page 22.

No new matter is added by these amendments.

Claims 3-6, 10, 21, 23, 32, 41, 42, and 46-58 are cancelled in response to the Examiner's final rejection under the restriction requirement of 24 September 2007.

II. Allowance of Claims 33, 38, and 43

Applicants gratefully acknowledge that Claims 33, 38, and 43 are allowed.

III. Election/Restriction

In response to the Office Action of 24 September 2007, applicants elected to restrict examination to Group I, Claims 1-45, drawn to compounds and compositions of formula I or II wherein either HET-1 or HET-2 (or both) is/are 1,3-diazine, with traverse. In the present Office Action, the Examiner finalized the restriction requirement and required cancellation claims 32, 41, 42, and 46-58 drawn to non-elected subject matter. In the interest of compact prosecution, applicants cancel claims 32, 41, 42, and 46-58 as requested by Examiner, and cancel claims 3-6, 10, 21, and 23 because they are also drawn to non-elected subject matter.

Inventorship is not affected by the cancellations.

IV. Oath and Declaration

The Examiner indicated that he marked item 11 in the Office Action Summary of 16 June 2008 because the Office had not received a signature from inventor Michael H. Fisher. Because inventor Michael H. Fisher is deceased, applicants submitted a Declaration and Power of Attorney (37 CFR 1.63) signed by Jeffrey M. Fisher as legal representative of the deceased inventor (35 USC 117) with the initial filing on 23 September 2005. On 29 June 2006, PCT Legal Examiner Rafael Bacares issued a decision that this declaration satisfied the requirements of 37 CFR 1.42. The 29 June 2006 decision is available in PAIR. In light of this decision, applicants request that the Examiner withdraw his objection.

V. Rejections under 35 U.S.C. § 112

Claims 1 and 37 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

In response to the Examiner's explanation, Applicants currently amend Claim 1 to correct typographical errors in the figures by replacing "R_1", "R_2", and "R_7" with "R^1", "R^2", and "R^7". Applicants also currently amend Claims 7-9, 22, and 24-31 to correct similar typographical errors in the figures.

Examiner stated that the definition of HET-2 in Claim 1 is unclear because "one of ordinary skill in the art would not necessarily be able to figure out which squiggly line represents the HET-1 side of the molecule and which squiggly line represents the phenyl side of the molecule." Applicants respectfully contend that the connectivity of HET-2 in Claim 1 is clear to one of ordinary skill in the art because the orientation of the heterocycles in the definition of HET-2 is the same as illustrated in Claim 1 formula II. One skilled in the art would read the definition of HET-2 from left to right and understand that the phenyl ring substituted with R^6, R^7, and R^8 is on the left and HET-1 is on the right.

Applicants also assert that the definition of HET-2 in Claim 1 is clear because the depicted heterocycles are either symmetrical about a central axis (first, second, third, and sixth of the eight possibilities) or both mirror images of unsymmetrical heterocycles are listed in the definition (fourth and eighth examples are mirror images; fifth and seventh

examples are mirror images). One skilled in the art would recognize that the symmetry of the depicted heterocycles makes the definition of HET-2 clear as written.

The Examiner noted an inconsistency in Claim 37 between "R^1" depicted in the figure and "R^2" indicated in the table. The table of Claim 37 has been amended to correct this typographical error.

VI. Rejections Under 35 U.S.C. § 102(a)

Claims 1, 2, 7, and 44-45 stand rejected under 35 U.S.C. § 102(a) as anticipated by Cao, et al. (WO 02/096867). Examiner states that Cao et al. teaches pyrimidinyl compounds, which include compounds of the present application, e.g. where R^1 is NR^aR^b, R^a and R^b are both hydrogen, R^2 and R^3 are both hydrogen, R^4 or R^5 is hydroxyl and the other is hydrogen, one of R^6, R^7, or R^8 is $-OR^a$ and the other two are hydrogen, and R^a is also hydrogen.

Applicants note that the relevant examples disclosed in Cao et al. are phenol-based compounds, wherein the "E_1R_{100}" substituent is a hydroxyl group (see, e.g., Cao et al., p. 10 and Examples 47, 50-57, 77-91, and 94). Accordingly, Applicants have amended Claim 1 to exclude compounds of the formula I in which one of R^4 and R^5 is 2-OH and the other is hydrogen, and one of R^6, R^7, and R^8 is $-OR^a$ in the para position while the other two are hydrogen, and said R^a is hydrogen. Applicants have also amended Claim 1 to exclude the compound 4-(4-aminophenyl)-6-(4'-methoxybiphenyl-3-yl)pyrimidin-2-amine disclosed on Cao et al p. 107. In view of this amendment, Claim 1 is not anticipated by Cao et al. Because Claims 2, 7, and 44-45 depend from Claim 1, these claims are not anticipated by Cao et al.

VII. Rejections Under 35 U.S.C. § 103

Claims 1, 14, 19, 29, and 44 stand rejected under 35 U.S.C. § 103(a) as obvious Katoh, et al., U.S. Patent No. 4,783,466 ('466). Examiner states that '466 teaches structurally similar pyrimidinyl compounds. While Examiner concedes that he could not find overlap between the Examples of the reference and Applicant's claimed compounds, he contends that the compounds disclosed by the reference "generically embrace the instant compounds" and that "[o]ne of ordinary skill in the art would be motivated to modify the compounds of Katoh et al. with other substituents to arrive at the instant pyrimidinyl compounds even though Katoh et al. used their compounds as plant disease

protectant instead of the instant use as sodium channel blockers for the treatment of CNS disorders."

A prima facie case of obviousness requires structural similarity between claimed and prior art subject matter and a showing of "adequate support in the prior art" for the change in structure to arrive at the claimed compounds. Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (internal citations omitted). This test is consistent with KSR, which requires identification of "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. Id. at 1356-1357, citing KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 1731 (2007).

Applicants respectfully note that the compounds disclosed by '466 are not structurally similar to compounds of instant Claim 19. '466 is directed at pyridinylpyrimidine derivatives in which the central ring of the three core rings is a pyridine ring ('466, column 1, lines 25-35). Claim 19 of the present invention is directed toward compounds in which the central ring, HET-2, is a pyrimidine. Thus, Claim 19 is patentable over '466 because the compounds disclosed in the reference are not structurally similar to the compounds of Claim 19.

Applicants also assert that the compounds disclosed by '466 are not structurally similar to the compounds of Claim 1 and do not "generically embrace" the compounds of the present invention. For example, on the pyrimidine ring of the generic structure disclosed in '466, substituents R^4 and R^5 can be hydrogen or C_{1-3} alkyl groups, and R^6 can be hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} alkylthio (column 1, lines 45-49). Contrastingly, the instant application discloses compounds in which pyrimidine HET-1 is substituted with, e.g., carboxylic acid, amide, amine, heterocycle, aryl, sulfone, and sulfoxide functional groups. These substituents are structurally diverse from those disclosed in '466.

Chemical obviousness requires that one skilled in the art would have had a reason to make specific structural changes to arrive at the compounds of the present invention, useful for the treatment of pain in mammals. See Takeda, 492 F.3d at 1356. Even if the compounds of the present invention were structurally similar to those disclosed in '466, the Examiner has not indicated any reason one would have been motivated by the disclosure in '466 to make the specific structural changes necessary to arrive at the compounds of the instant invention.

Also, obviousness requires that the skilled artisan would have had a reasonable expectation of success in making a suggested modification. Pfizer v. Apotex, 450 F.3d 1348, 1361 (Fed. Cir. 2007). Here, the Examiner has not stated why one skilled in the art would have reasonably expected that modifying the fungicidal compounds of '466 to arrive at the compounds of the present invention would produce sodium channel blockers useful for the treatment of pain in mammals.

Even if the Examiner contends that suggestion or motivation is implicit in the prior art, the Examiner must support his contention with "particular findings" rather than "conclusory statements." See, e.g., In re Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000). An examiner's assessment of "basic knowledge" or "common sense" still requires supporting evidence in order to be the basis of an obviousness rejection. In re Zurko, 258 F.3d 1379, 1385 (Fed. Cir. 2001).

Thus, Applicants respectfully contend that the claims at hand are nonobvious over '466 and request reconsideration of Claims 1, 14, 19, 29, and 44.

The Examiner also rejected Claims 1, 12, 19, 24, and 44 as obvious in view of Katoh et al., U.S. Patent No. 4,873,248 ('248), which teaches pyridinylpyrimidine compounds with fungicidal properties useful for curing and controlling plant diseases. Examiner concedes that he did not find overlap between the Examples of '248 and Applicant's claimed examples, but asserts that the compounds disclosed by the reference generically embrace the instant compounds where HET-1 is pyridine and HET-2 is pyrimidine. He also contends that "[o]ne of ordinary skill in the art would be motivated to modify the compounds of Katoh, et al., with other substituents to arrive at the instant pyrimidinyl compounds even though Katoh, et al. used their compounds as fungicide instead of the instant use as sodium channel blockers for the treatment of CNS disorders."

Applicants respectfully reply that the compounds of the present invention are not obvious over '248 because they are structurally distinct. '248 discloses pyridinylpyrimidines in which the central pyrimidine ring can be substituted with R^5, chosen from hydrogen and lower alkyl, and R^6, selected from hydrogen, lower alkyl, alkoxy, alkenyloxy, and alkylthio groups. The pyridine ring can be substituted with R^1, which is lower alkyl, and R^2 and R^3, which are chosen from hydrogen and methyl. The R^4 substituents on the phenyl ring are selected from lower alkyl, lower alkoxy, and lower haloalkyl. Contrastingly, instant Claim 1 discloses compounds in which the HET-1 pyridine ring can be substituted with structurally diverse groups such as carboxylic acid, amide, amine, heterocycle, aryl, sulfone, and sulfoxide functional groups. The central HET-2 pyrimidine ring may be substituted with functional groups such as halo,

fluoroalkoxy, benzyloxy, and acetamide, which are structurally different from the substituents disclosed in '248. Additionally, the phenyl ring in compounds of formula II of Claim 1 may be substituted with, e.g., fluoroalkyl or fluoroalkoxy groups that are structurally distinct from those substituents disclosed in '248.

Even if the compounds of '248 and the present invention were structurally similar, the Examiner has not cited any support for his assertion that one skilled in the art would have been motivated by the disclosure of '248 to make the specific modifications necessary to arrive at the compounds of the present invention. Nor has he cited any reason why one would have had a reasonable expectation, based on the disclosure of fungicidal properties in '248, that the instant compounds would be sodium channel blockers useful for the treatment of pain in mammals.

Finally, Claim 44 is directed to a pharmaceutical composition comprising a therapeutically effective amount of the compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier. Given that '466 and '248 describe fungicidal compositions of the disclosed compounds, Applicants assert that these references would not have given one skilled in the art reason to prepare pharmaceutical compositions of the structurally diverse compounds of the instant application.

VIII. Objections

The Examiner objected to Claims 3-6, 8-11, 13, 15-18, 20-23, 25-28, 30-31, 34-36, and 39-40 as being dependent on rejected independent Claim 1 but otherwise allowable if rewritten in independent form.

Applicants note that Claims 3-6, 10, 21, and 23 are currently cancelled because they are drawn to non-elected subject matter.

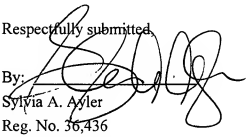
Based on the foregoing remarks, Applicants believe Claim 1 is in condition for allowance and therefore request reconsideration of Claims 8, 9, 11, 13, 15-18, 20, 22, 25-28, 30, 31, 34-36 and 39-40 as written.

IX. Conclusion

In light of the amendments and remarks herein Applicants believe the claims are in condition for allowance. The Examiner is respectfully requested withdraw

the objections and 35 USC sections 112, 102(a), and 103(a) rejections and to contact the undersigned at the number below if this would expedite the allowance.

Respectfully submitted,

By: 

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